Protection for Human Subjects in Medical Research

To the Editor: Dr Woodward[1] cites 1 study to generalize a claim that institutional review boards (IRBs) are overtaxed with protocols and spend only a cursory amount of time reviewing studies. My personal experience with 3 review boards, including 4 years of recent experience as an IRB member, goes against this. Under our current IRB rules, each study is reviewed in depth by 2 people, sometimes 3. This takes from a few minutes to an hour. At the IRB meeting, discussions of a well-constructed study without consent issues require 5 to 10 minutes. Studies with poor consent design or problems relating to their underlying science have taken over 45 minutes to resolve, often with a requirement that the investigator reply to criticisms at a later meeting. Our level of review is careful, and our IRB chair has explicitly defined our duty to protect research subjects.

Is our IRB overtaxed? This depends on what the public expects of research professionals. We choose to remain on the IRB out of a sense of responsibility, as the local "cop on the beat" to protect both subjects and researchers. Reviewing studies is done away from the office, and it is certainly an imposition on the family lives of reviewers. Institutional review board meetings increasingly compete with patient care demands, and moving IRB meetings to the end of the day does not eliminate the problem of achieving a quorum of members when the hospital is very busy. Fortunately, our IRB is chaired by an experienced researcher who keeps the members away from the most onerous paperwork. If the hospital or IRB sponsor does not adequately support the research director, the IRB will not work and research subjects will not be protected.

In his Editorial, Dr Ellis[2] misses a major point in calling for studies to determine unmet needs of IRB members. Why not pay the members? Every academic center IRB with which I have experience has expected the scientist and physician members to donate their time and expertise. Is our time away from clinical services not worth something? I believe that even a small payment for the time it takes to review studies would not overtax the research infrastructure of this nation, and it would go far in alleviating some of the burden for IRB members. It is no longer acceptable to assume that if we are on a teaching faculty that our services to committees, such as the IRB, are included in our salary structure, especially when much of the critical work is done at home in the evening hours.

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1. Woodward B. Challenges to human subject protections in US medical research. *JAMA*. 1999;282:1947-1952.
2. Ellis GB. Keeping research subjects out of harm's way. *JAMA*. 1999;282:1963-1965.

To the Editor: Dr Woodward[1] notes that there are efforts under way to alter US federal regulations that govern medical research, and she expresses concern that these changes may be influenced by pressures that "subordinate the interests of the subject to those of science and society." Her fears may be justified and should be heeded. However, I take issue with her argument that the concept of "minimal risk" is a prime victim in this scenario and that it is critical to the health of the current system for protecting human subjects. I would like to propose that it is, instead, one of the causes of the illness.

Minimal risk as defined in the 1991 document generally referred to as the "Common Rule,"[2] does not appear as such in either the Nuremberg,[3] Helsinki,[4] or Belmont[5] documents. It is a relatively recent notion that is born of the mistrust of the integrity of researchers and of the misguided belief that abuses can be prevented by all-inclusive federal regulations. The terms *research* and *human subject* are so broadly defined in the Common Rule that it necessitated a mechanism to deal with the inevitable burgeoning of protocol reviews. Thus, research classified as "minimal risk" could qualify for expedited review (review by a single person instead of a full IRB) or for exemption from the informed consent requirement.

As defined in the Common Rule, *minimal risk* means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." It can be argued that not every activity that fits this description needs to be considered "human research." It is incongruous to require a protocol, IRB review (expedited or not), and consent form for an activity that involves less risk than driving the roads that take the "human subject" to the laboratory. (This position does not ignore the confidentiality issue, which, in my view, should be dealt with separately from the risk of direct physical or psychological harm to the subject).

The well-conceived, well-intentioned, and time-honored Nuremberg and Helsinki documents should remain intact. Informed consent should remain inviolate except under the most

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unusual circumstances. It is the Common Rule, with its vague but overly restrictive guidelines, that should be reexamined. As written, it has created the potential for widespread noncompliance and for pressures to alter fundamental human research tenets, such as informed consent.

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Disclaimer: The views expressed are those of the author and do not necessarily reflect those of the National Aeronautics and Space Administration.

1. Woodward B. Challenges to human subject protections in US medical research. *JAMA*. 1999;282:1947-1952.
2. 45 CFR §46:102(1991).
3. The Nuremberg Code. *JAMA*. 1997;276:1691.
4. World Medical Association Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *JAMA*. 1997;277:925-926.
5. Department of Health, Education and Welfare. The Belmont Report: Ethical Principles and Guidelines for Protection of Human Subjects of Research. Bethesda, Md: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; April 18, 1979.

To the Editor: I suspect that many investigators were surprised by Dr Woodward's[1] claim that human research subjects are now threatened with increasing risks because of pressures to reduce the protections offered by current procedures for reviewing and approving research protocols. On the contrary, the system created to assure that we protect human research subjects is increasingly difficult to navigate, with little evidence of a commensurate increase in the protection of human subjects. Furthermore, I believe it is the manner in which existing regulations are being interpreted and enforced that is creating some of the problems described by Woodward, particularly the increasing inability of IRBs to handle the avalanche of protocols they now receive.

Specifically, federal funding agencies interpret the regulations to require that all "performance sites" review and approve a research protocol before funds will be dispersed, even if the result is that scores of review boards at various enrollment sites review the same protocol. The resulting burden on such review boards has, not surprisingly, multiplied substantially, and the resulting challenge to the investigator can be almost insurmountable. Various IRBs invariably have minor but maddeningly different formats for submission of protocols; want different wording of consent forms and study explanations; insist on different letterhead for study documents; and sometimes disagree over more substantive issues relating to subject recruitment, compensation, etc. Anyone who has juggled the conflicting demands of multiple review boards in an effort to gain approval from all of them knows how arduous and time-consuming the process can be. Is there a commensurate increase in the level of protection offered to participants in such studies, beyond what would be achieved by having a single IRB review the protocol? It seems doubtful that there is, particularly when many such studies involve nothing more than the administration of a questionnaire, in which the only "risks" are possible embarrassment about sensitive questions and the burden of responding.

If the current system is inadequate to protect research subjects being recruited into clinical studies, where the risks often are tangible and substantial, then perhaps part of the solution is for IRBs to give more attention to such protocols and spend less time rereviewing protocols that have been approved by other boards. In a rational system, approval of a protocol by 1 review board would be sufficient, particularly when the research does not involve any invasive procedures.

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1. Woodward B. Challenges to human subject protections in US medical research. *JAMA*. 1999;282:1947-1952.

To the Editor: Both Dr Woodward's[1] article and Dr Ellis' Editorial are based on the premise that patients are at risk of having their protection "eroded" when they sacrifice themselves by participating in randomized clinical trials. The former author decries "new pressures to subordinate the interests of the subject to those of science and society," and the latter quotes from Katz et al, "When may a society . . . expose some of its members to harm in order to seek benefits for them, for others, or for society as a whole?" Even *JAMA* assumes that patients may be harmed in randomized clinical trials by offering continuing medical education credit for those who read Woodward's piece based on the educational objective: "To understand how medical research may threaten human subject protections."

While I staunchly defend the autonomy and other rights of individuals in trials (surely it's time for all of us, including Dr Woodward, to stop referring to them as "subjects"), I'd nonetheless like to pose 4 simple questions to Woodward and Ellis.

1. Did either of them carry out a systematic review of the biomedical literature to determine if there was an evidence base for their premise that patients in randomized trials are at increased risk? (To borrow their words, "have they kept up with their science?").

2. Are they aware that more than 90% of this evidence base shows that patients in randomized trials fare better (eg, lower death rates,[2-4] lower risk of cholera,[5] and less neonatal morbidity[6]) than similar patients treated outside of trials? (I have found 21 such studies [available at http://hiru.mcmaster.ca/ebm/trout] and would appreciate hearing from anyone who has additional citations or wants to join the proposed Cochrane review on this topic.).

3. Do they think that this evidence base ought to be required reading for ethics committees?[7]

4. If, on reviewing this evidence base, they agree that patients in trials, on average, fare better than similar patients treated outside of trials, would they agree that future patients contemplating joining randomized trials deserve, under the principle of informed consent, to be supplied with this information?

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1. Woodward B. Challenges to human subject protections in US medical research. *JAMA*. 1999;282:1947-1952.

2. Davis S, Wright PW, Schulman SF, et al. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. *Cancer.* 1985;56:1710-1718.
3. Stiller CA. Centralized treatment, entry to trials and survival. *Br J Cancer.* 1994; 70:352-362.
4. Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and non-participants: a population-based comparison. *J Am Coll Cardiol.* 1996;27:1335-1342.
5. Clemens JD, van Loon FF, Rao M, et al. Nonparticipation as a determinant of adverse health outcomes in a field trial of oral cholera vaccines. *Am J Epidemiol.* 1992;135:865-874.
6. Schmidt B, Gillie P, Caco C, Roberts J, Roberts R. Do sick newborn infants benefit from participation in a randomized clinical trial? *J Pediatr.* 1999;134:151-155.
7. Chalmers I, Lindley R. Double standards on informed consent to treatment: ignored for a quarter of a century by most professional medical ethicists. In: Doyal L, Tobias JS, eds. *Informed Consent: Respecting Patients' Rights in Research, Teaching and Practice.* London, England: BMJ Publications. In press.

To the Editor: Dr Woodward's[1] article draws incorrect conclusions from 2 reports[2,3] published by the National Bioethics Advisory Commission (NBAC).

We are puzzled by Woodward's comment that "NBAC has recently taken steps both to strengthen and to weaken the consent requirement," referring to the report on decision-making capacity[2] as an instance of the former and the report on human biological materials[3] as an example of the latter. When advising the president, NBAC does not presume that its role is always to recommend stricter (or looser) protections. It is not, as Woodward claims, a "noteworthy departure" for NBAC to have resolved as a matter of principle that "no person should be enrolled in research without the twin protections of informed consent and independent review of the research," nor to have recommended that federal regulations be changed to allow IRBs to grant waivers of the consent process even if it is practicable to obtain consent. Like any comprehensive ethical analysis, NBAC's reports begin with no such presumptions; rather, we identify the relevant issues, the context in which the issues occur, and the relevance of particular ethical considerations and principles. Indeed, we consider it a virtue of this commission that the deliberations on these 2 very different topics—the involvement of persons with specific mental disorders and the use (rather than involvement) of tissue specimens remaining from medical and surgical procedures—could lead to different conclusions and recommendations regarding the adequacy of existing federal protections.

We are grateful that NBAC's work has generated the kind of careful analysis and assessment that Woodward intended to provide. However, it is important that such analyses reflect both the spirit and substance of the commission's work.

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1. Woodward B. Challenges to human subject protections in US medical research. *JAMA.* 1999;282:1947-1952.
2. National Bioethics Advisory Commission. *Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity.* Rockville, Md: National Bioethics Advisory Commission; December 1998.
3. National Bioethics Advisory Commission. *Research on Human Biological Materials: Ethical Issues and Policy Guidance.* Rockville, Md: National Bioethics Advisory Commission; August 1999.

In Reply: Dr Kaufman indicates that his current IRB is able to devote enough time to provide a careful review of each study that comes before it. This is not inconsistent with the claim that many IRBs are overtaxed. A recent study undertaken for the National Institutes of Health surveyed 491 multiple project assurance IRBs and found that the "49 highest-volume IRBs accounted for 34,500 initial reviews, 34 times more than the 1,000 reviews conducted in the 49 lowest-volume IRBs."[1]

I agree with Dr Pelligra that there are problems in interpreting and applying the concept of minimal risk. However it is not an activity's degree of risk that determines whether it is research but whether the activity is "designed to develop or contribute to generalizable knowledge." It should not be left to researchers to exempt their own activities from review on the basis of personal judgments about the degree of risk in the activity.

I am sympathetic with Dr Reingold's view that it is desirable to have a more centralized system of review for multisite studies. I believe it is important, however, that such a system allow for some kind of input by local IRBs. I disagree with his view that "possible embarrassment" is a trivial risk for a research subject.

Dr Sackett wants me to review the "evidence base" regarding harms and benefits to research subjects. Unfortunately, such an evidence base is not available. There is no comprehensive publicly available database of adverse event reports; moreover, not all adverse events are reported.

Drs Shapiro and Meslin defend NBAC's recommendation "that federal regulations be changed to allow IRBs to grant waivers of the consent process even if it is practicable to obtain consent" for research using already existing human biological materials. They argue that the distinction between "the involvement of persons" in research and "the use (rather than involvement) of tissue specimens" justifies NBAC's differing recommendations on consent processes for research involving persons with mental disorders and for research using human tissue specimens. NBAC's recommendation on tissue research, however, applies to tissue specimens that are coded (ie, identifiable) or identified, so persons *are* involved, and in the case of genetic research, not just the person who is the tissue source is involved, but family members as well. To be sure, genetic research and other innovative research may be judged not to pose minimal risk and therefore not come under NBAC's recommendation. But judgments about minimal risk are highly variable, so this concept provides little protection for the identifiable individuals whose tissues are being studied. Moreover, researchers who will use prospectively collected specimens may ask why the practicability of obtaining consent should be a factor in NBAC's recommendation that consent be obtained for all such research, even minimal-risk research, if NBAC believes that practicability is irrelevant in deciding about waiv-

ers of consent for (virtually identical) research with already existing specimens.

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1. Bell J, Whiton J, Connelly S. *Final Report: Evaluation of NIH Implementation of Section 491 of the Public Health Service Act: Mandating a Program of Protection for Research Subjects.* June 15, 1998:9. Available at http://grants.nih.gov/grants/oprr/hsp_report/hsp_final_rpt.pdf. Accessed March 30, 2000.

These letters were shown to Dr Ellis, who declined to reply.—ED.

How Should Physicians Involve Patients in Medical Decisions?

To the Editor: Dr Braddock and colleagues[1] found that 91% of patient-physician interactions failed to meet their definition of informed decision making. However, this snapshot approach ignores the context of the patient-physician relationship. Every intervention is negotiated with each patient, and both sides have expectations based on prior interactions, which lay the groundwork for a productive relationship. Each interaction, however, must stand on its own merits. If we fail the patient's expectations this time, next time we have to rebuild or the patient will need to start over somewhere else. Patients become comfortable with a relationship, which varies in its paternalism or autonomy depending on the decision at hand. Trust, therefore, is earned. Without it we have to go through a cumbersome decision framework bit by bit, warily sparring back and forth until there is a comfort level of trust.

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1. Braddock CH III, Edwards KA, Hasenberg NM, Laidley TM, Levinson W. Informed decision making in outpatient practice: time to get back to basics. *JAMA.* 1999;282:2313-2320.

To the Editor: The article by Dr Braddock and colleagues[1] has been useful in our new course on health communication, especially the table listing the 7 elements of informed decision making. From a statistical standpoint, however, we are concerned that the unit of analysis was the individual clinical decision. The analysis used *t* tests, χ^2 tests, and Fisher exact tests, all of which require independent observations. Individual physicians and patients all have past experiences, personalities, and dispositions that result in preferences for certain styles of communication. For example, a physician who has developed a heightened awareness of the importance of good communication may practice more complete, informed decision making with all patients. The physician may therefore be a more appropriate unit of analysis than the individual clinical decision.[2] On the other hand, patients who take a more active role in the encounter probably elicit more complete information from the physician. When studying the complex process of communication[3] within this type of sample, it is important to control for the individual patient and physician when testing for differences in various communication elements in the clinical visit.

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1. Braddock CH III, Edwards KA, Hasenberg NM, Laidley TM, Levinson W. Informed decision making in outpatient practice: time to get back to basics. *JAMA.* 1999;282:2313-2320.
2. Whiting-O'Keefe QE, Henke C, Simborg DW. Choosing the correct unit of analysis in medical care experiments. *Med Care.* 1984;22:1101-1114.
3. Kreps GL, Thornton BC. *Health Communication: Theory and Practice.* 2nd ed. Prospect Heights, Ill: Waveland Press Inc; 1992.

To the Editor: We wish to suggest an entirely different interpretation of Dr Braddock and colleagues'[1] dismal finding that physicians failed to meet a standard for informed consent 91% of the time. Rather than indicting physicians, these findings challenge the standards themselves.

In recent decades, studies like those of Braddock et al have established that the practice of informed consent is far removed from its theory. Meanwhile, ethicists have crept toward what could be called mandatory autonomy—the view that patients should make their own decisions whether they want to or not.[2] In other words, ethicists have increasingly made the standards for informed consent more stringent even as empiricists have increasingly shown how rarely they are met.

Why such dismal results, after so many years of ethical admonition and adjuration? Braddock et al, like many others, assume the standards are correct and that physicians are wrong. However, many studies find that patients are generally satisfied with how their physicians communicate with them.[2,3] When the standards used to judge physicians conflict so persistently with what so many competent physicians actually do and so many thoughtful patients accept, it is time to reconsider the standards themselves.

Today's standards assume that patients usually should make their own medical decisions based on a thorough understanding of each plausible treatment. Thus, Braddock et al present an approach that suggests the "need for some dialogue about virtually every clinical decision," requiring 7 layers of discussion for even routine decisions, to allay the fear that patients may "adopt a passive or nonparticipatory style." But there are excellent reasons to believe that patients may rationally decide to delegate decisional authority to their physicians and to forgo technical expositions, elaborations, and equivocations.[3] Certainly, this is not true for all patients, but should not individual patients' actual preferences, rather than the abstractions of ethicists, be the criterion standard for evaluating physicians?

Of course physicians' communication skills can and should be improved. But physicians also receive directives from other communication researchers and ethicists (eg, to explore the psy-